IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Gleave, et al.	
Application No.: 09/913,325	Group Art Unit: 1635
Filed: 8/10/2001	Examiner: Tracy Vivlemore
Title: TRPM-2 Antisense Therapy	Confirmation No: 8469
Attorney Docket No.: UBC.P-020	
Customer No.: 57381	

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL REJECTION

Dear Sir:

This is in response to the Office Action mailed March 30, 2006 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Applicants request an extension of time sufficient to make this paper timely and enclose the fee.

The Examiner rejected claims 6, 8, 10, 12-17, 31 and 32 under 35 USC § 103 as obvious over the combination of Bruchovsky, Sensibar, Kyprianou and Raghavan. The Examiner asserts, *inter alia*, that the statement in Bruchovsky (Page 20) suggesting anti-TRPM-2 gene therapy in combination with androgen withdrawal or replacement in combination with the teaching of Sensibar of an antisense targeted to TRPM-2 render the claimed invention of independent claim 6 obvious. Applicants respectfully disagree.

Obviousness under 35 USC § 103 requires something more than just locating the pieces in the art. As explained by the Court of Appeals for the Federal Circuit,

> The consistent criterion for determining obviousness is whether the prior art would have suggested...that this process should be carried out and would have a

> reasonable likelihood of success...Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure .

In re Dow Chemical, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Here, the statement that the Examiner relies upon in Bruchovsky is not a basis for finding an expectation of success, but rather a description of future directions for research to be undertaken to find out what happened. Indeed, it is found in the section labeled "Future Directions."

Applicants enclose a Declaration under Rule 132 by Martin Gleave, who is both an inventor of this application and an author of the Bruchovsky paper. In this declaration, Dr. Gleave explains that:

> At the time Bruchovsky et al. was written, we, as the authors of the paper, intended this as an indication of the direction that our research would take, and not as a statement that anti-TRPM-2 would necessarily provide a therapeutic benefit. Further, as a researcher studying this area, I would not understand this passage to provide an expectation of any particular result from the proposed experiments once performed. At that time, it simply was not known whether a decrease in TRPM-2 levels would cause or prevent apoptosis.

Declaration, ¶ 3. He further declares that this uncertainty existed until the time of the experiments that are the basis of the present application. ¶ 4.

Examples of this uncertainty can be found in the very art that the Examiner relies upon. For example, in Sensibar et al. cited by the Examiner, the statement is made that the prior observations in the literature "have left the possibility of [TRPM-2] being associated with prostatic cell death questionable; much less certain is the role of [TRPM-2] in cell death." (page 2431, Col. 2). ¶ 5. As explained by Dr. Gleave, the reasons for the conflicting results with respect to the function of TRPM-2 (clusterin) is now known, namely that

> there are different isoforms of clusterin with different functions, and this fact contributed to the ambiguity in findings prevalent at that time. Briefly, a nuclear form of CLU protein (nCLU) promotes apoptosis, and a secretory form (sCLU), promotes survival.

¶ 5. Since antisense could well target either the nuclear form or the secretory form of TRPM-2 or both, there was no way to predict with any reasonable expectation of success, what the actual result of the experiment proposed in the Bruchovsky paper would be.

Because the statement in Bruchovsky is plainly a description of a planned experiment, and because the function of TRPM-2 was unclear at the time this application was filed, Applicants submit that the combination of Bruchovsky and Sensibar does not render the present application obvious. The additional references relate to features of dependent claims, and therefore do not overcome this fundamental deficiency. Accordingly, Applicants submit that the rejection of claims 6, 8, 10, 12-17, 31 and 32 is in error and should be withdrawn.

Applicants further submit that the Examiner has overstated the relevance of the Raghavan reference in citing it against claims reciting additional treatment with chemotherapeutic agents, and that the rejection of claims 12, 13, 16, 17 and 31 is in error for this additional reason. The Examiner states that Raghavan teaches use of cytotoxic agents such as mitoxanthrone in the treatment of prostate cancer, and further teaches that "taxanes such as paclitaxel have promising activity in combination therapies." With respect to the latter, what the reference actually states is that paclitaxel has "promising activity" when it is "combined with other spindle inhibitors." (Page 570, Col. 2.) Thus, Raghavan offers no teaching or suggestions with respect to combination therapies generally.

Furthermore, Applicants submit that nothing in the art suggests the superior effectiveness of combinations that include the both antisense therapy and a chemotherapeutic agent. As shown in the attached declaration, there was essentially no difference in tumor volume of PC-3 prostate cancer cells between mice treated with antisense alone or the mismatch control. On the other hand, treatment with a chemotherapy agent (taxol or mitoxanthrone) and the mismatch control oligonucleotide resulted in much smaller tumors (solid symbols). Even better results were obtained using the antisense in combination with the chemotherapy agent (open symbols), notwithstanding the fact that the antisense alone did not improve the performance relative to the mismatch control alone. Nothing in the art suggests this synergy. Accordingly, claims which recite an additional chemotherapeutic agent are unobvious for this additional reason.

For the foregoing reasons, Applicants submit that this application is in form for allowance. Favorable reconsideration and allowance of all pending claims are respectfully urged.

Respectfully submitted,

/marina/
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Enclosure: Declaration Under Rule 132